REMARKS

I. INTRODUCTION

The Specification has been amended. Claims 31-40 have been amended. Claims 1-30 were previously cancelled. Claims 41-67 were withdrawn. Thus, claims 31-67 are pending in the present application. No new matter has been added. In view of the above amendments and the following remarks, it is respectfully submitted that claims 31-40 are in condition for allowance.

II. THE RESTRICTION REQUIREMENT SHOULD BE WITHDRAWN

Applicants maintain the position that the claims are of a single general inventive concept under PCT Rule 13.1.

A common technical feature among the Groups I-X is the culture medium comprising: a) 0.1%-90% autologous human serum, b) 0.1%-10.000% Ul/ml heparin, c) 0.1%-10.000% Ul/ml protamine, and d) a base culture medium including nutrients. The Examiner maintains that this common technical feature is an obvious variant of a known composition described in Xia et al., The Journal of Immunology, p. 1134, Fig. 5 (hereinafter "Xia"). However, it is respectfully maintained that the Restriction Requirement is in error for the following reasons.

Initially, it was previously submitted that, according to 37 CFR 1.475, a special technical feature is any common element that defines a contribution over the prior art. Accordingly, the culture medium described above greatly contributes to the technical advancement of the field of *isolation and expansion of cultured autologous human progenitor stem cells*. Previously (*i.e.*, before the priority date of the present application), it was technically challenging to isolate or expand autologous human stem cells in culture. However, according to the claims of the present application and thorough experimental procedures described in the present application, improved results of using the above described culture media for expanding autologous human stem cells is realized.

The Examiner replies to the above argument by defining the intended use of the claimed composition only requires that the composition be suitable for the culture of progenitor cells which the Xia media composition is used. (See 7/18/08 Office Action, p. 2). However, it is respectfully submitted that the Examiner has broadened the intended use beyond acceptable provisions provided by 37 CFR 1.475. In fact, as stated above and cited directly from the statute, 37 CFR 1.475 explicitly recites that the "expression 'special technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." That is, the "contribution" that the claims of the present invention relates to the culture of progenitor cells, but more specifically, to the *isolation and expansion of cultured autologous human progenitor stem cells*. Thus, it is respectfully submitted that the Examiner has incorrectly defined the intended use of the claims of the present invention to a generalized whole when the contribution is clearly defined throughout the Specification and the claims to the isolation and expansion of the progenitor stem cells.

Furthermore, it is noted that claims 31-40 have been amended in the preamble to further emphasize that the present invention is not directed merely to any use of a culture medium. That is, claims 31-40 have been amended to stress that the culture medium is used for at least expansion purposes, as discussed above. Support for this amendment may be found throughout the entire Specification. (*e.g.*, See Specification, ¶ [0001]).

In addition, it was previously submitted that Xia provides an improper basis for the restriction. Specifically, the authors of Xia use a heparin-containing media for the differentiation of monocytes based on the premise that there are specific heparin-binding receptors on the surface. That is, Xia discloses the culture of human monocytes in a medium (AIM-V) containing autologous serum (2%) with heparin (25 UI/ml) and protamine sulphate (0.125 mg/ml). However, those skilled in the art will understand that monocytes are *not* progenitor stem cells. Other assays disclosed in Xia use dendritic cells to examine the effect of heparin-induced differentiation on their physiology (*i.e.*, production of IL-10 and priming of naïve CD4+ cells). However, those skilled in the art will also understand that dendritic cells are *not* progenitor stem cells. Therefore, the use of heparin in Xia is related to its capacity to promote differentiation of monocytes into CD1a+ dendritic cells. Protamine sulphate, a heparin-binding protein, is used

here for neutralization of heparin in order to understand the mechanisms mediating heparin-dependent differentiation. Hence, motivations to use heparin and protamine in the culture media of Xia run contrary to the motivations for using the culture media disclosed in the present application. Also, differentiation and expansion (relating to proliferation) are fundamentally opposed biological processes and, therefore, Xia strongly sets out a prejudice for the use of the culture media of the present application for cell expansion, thereby providing anything but an obviating disclosure. The Examiner explicitly states (regarding the previously described argument above) that the intended use is for the culture of *progenitor* cells. The Examiner appears to reply to the above argument by merely stating that because the same "ingredients" are used between the claims of the present invention and the media of Xia, they are obvious variants of each other. However, the Examiner does not appear to provide a response to the above argument relating to monocytes and dendritic cells. Therefore, it is respectfully maintained that Xia provides an improper basis for the restriction.

Furthermore, it was previously presented that, contrary to Xia, the present application does not use heparin to manipulate cell physiology. According to the present application, heparin is used as an anticoagulant in the plasmapheresis and protamine sulphate is used to reverse anticoagulation. In this manner, the use of the serum obtained from plasmapheresis with heparin and protamine enables blending with culture media without subsequent problems during cell culture. Also, heparin is used in the culture medium instead of anticoagulants which are traditionally used during plasmapheresis. In the present application, plasmapheresis is the process of choice for obtaining autologous human serum. However, in Xia, the method for obtaining autologous human serum is not disclosed, neither is there any indication suggesting the role that heparin plays in the present application. The Examiner does not appear to address this previously submitted argument. Instead, the Examiner appears to negate this previously submitted argument by merely using the fact that the same "ingredients" are used between the claims of the present invention and the media of Xia. However, those skilled in the art will understand that the mere coincidence that common "ingredients" (which happen to be in different concentrations) are used does not obviate the purposes for including heparin and protamine sulphate.

Accordingly, in view of the above reasons, it is respectfully submitted that the restriction is improper. It is therefore respectfully requested that the restriction requirement be withdrawn and the claims be examined on the merits.

III. THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The Examiner objected to the Specification for an informality. Specifically, page 9 of the Specification, which includes paragraphs [0053]-[0058] are disclosed in Spanish. (See 7/18/08 Office Action, p. 3). The Specification has been amended to delete paragraphs [0053]-[0058]. Thus, it is respectfully submitted that the Examiner should withdraw the objection to the Specification.

IV. THE 35 U.S.C. § 112 REJECTION SHOULD BE WITHDRAWN

The Examiner has rejected claims 31-40 under 35 U.S.C. § 112, second paragraph, as being indefinite. (See 7/18/08 Office Action, p. 3).

The Examiner rejects claim 31 for reciting limitations that are different units of concentration and, therefore, the range is unclear. Claim 31 has been amended to remove the % sign. Thus, claim 31 recites "between 0.1 and 10.000 UI/ml heparin" and "between 0.1 and 10.000 UI/ml protamine." Support for these amendments may be found in the Specification at least on p. 2, paragraph [0030] and Example 1. Therefore, it is respectfully submitted that these ranges are clear.

The Examiner also rejects claim 31 for reciting "basic nutrients" which Examiner asserts is not defined. However, it is respectfully submitted that "basic nutrients" is at least implicitly defined and, even if not explicitly defined, those skilled in the art will understand what "basic nutrients" are referred in the context of the present invention. Initially, the Specification at least implicitly defines "basic nutrients" to be "furnished by the medium HAM F12 [GIBCO BRL]." (See Specification, p. 2, ¶ [0028]). Furthermore, those skilled in the art will understand that in the art of culturing mammalian cells, the expression "basic nutrients" refers to all essential nutrients. Essential nutrients are those which cannot be synthesized by an organism and are required to be supplied by feeding. In addition, it is noted that for mammalian cells, the essential

nutrients include all of the 20 amino acids from which proteins are synthesized; a purine and a pyrimidine for the synthesis of nucleotides as well as respective polymers of DNA and RNA; phospholipids precursors; vitamins; lipoic acid; glucose and the inorganic ions NA^{+}, K^{+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, and CO^{2+}. Therefore, it is respectfully submitted that "basic nutrients" is implicitly defined and known to those skilled in the art.

The Examiner rejects claim 39 for reciting ingredients whose ingredients result in over 100% when added to the composition of claim 31. Claim 39 has been amended to properly recite the intended language. Specifically, claim 39 relates to an embodiment of the expansion culture medium that comprises the composition disclosed therein. Furthermore, the composition includes a sum resulting in 100%. Thus, it is respectfully submitted that claim 39 is clear. It is noted that claim 40 has also been amended to address the amendment to claim 40.

The Examiner rejects claims 39-40 for including limitations that use an improper preposition, thereby making the language of claim 39 indefinite. Claims 39-40 have been amended in a manner substantially following the Examiner's suggestion. Specifically, claims 39-40 recite ranges for the components of the autologous human serum. Thus, it is respectfully submitted that claims 39-40 are clear.

V. THE 35 U.S.C. § 103(a) REJECTION SHOULD BE WITHDRAWN

The Examiner rejects claims 31-37 under 35 U.S.C. § 103(a) as unpatentable over The Journal of Immunology, Xia et al., 2002 (hereinafter "Xia").

Initially, it is again noted that claims 31-40 have been amended in the preamble to emphasize the present invention is directed toward the *expansion* of a culture medium. That is, the present invention is not merely directed toward any use of the culture medium. The claims of the present invention relate to the field of progenitor stem cell expansion. The state of the art of expanding progenitor stem cells is such that culturing typically requires the absence of differentiating factors and the presence of specific cell factors. In fact, strong efforts have been invested in identifying these expansion factors. However, it has never been possible to expand cells in the presence of differentiating factors. Heparine, as used in Xia, is a differentiation

factor. Field grounding studies demonstrate that, upon differentiation, cells stop proliferating and synthesizing DNA and, therefore, expanding (even though synthesis of RNA may still occur). Xia is not concerned with the problem of *expanding* progenitor stem cell cultures. IN contrast, the work described in Xia relates with cell differentiation where the state of the cells precludes proliferation of the cells, DNA synthesis and cell expansion.

Applicants would like to thank the Examiner for reminding the Applicants of the law behind 102 and 103 rejections relating to product-by-process claims. The Examiner emphasizes that, regardless of the process to make a product, so long as the product is substantially similar between the prior art and the pending application, a rejection based upon 102 or 103 is "eminently fair and acccptable." However, Applicants would like to take this opportunity to rely upon MPEP 2145.01 which states that in order to rely on a reference under 103, it must be analogous prior art. MPEP 2145.IX states that a prior art reference is analogous if the reference is in the field of the applicant's cndeavor or if the reference is reasonably pertinent to the particular problem with which the inventor was concerned. As discussed above, the Applicants' endeavor or the particular problem with which Applicants were concerned relates to the *expansion* of progenitor stem cell cultures. Consequently, it is respectfully submitted that Xia is *not* in the field of endeavor of the present application. Cell biology is a vast field of knowledge that may be divided into multiple fields of technology including cell signaling, vesicle trafficking, cell motility, cell growth, cell differentiation, etc. Thus, cell differentiation may not be applied, for example, in the field of cell motility. Accordingly, art developed in the field of cell differentiation may not be applied in the field of cell expansion because the molecular and subcellular elements involved are incompatible and unable to perform both functions at the same time. In fact, those skilled in the art will understand that the differentiation of cells makes it impossible for the replication of DNA because DNA is organized in highly packed structures called heterochromatin. Genes locked in heterochromatin structures are not to be expressed. During the S-phase of the cell cycle, heterochromatin areas are not accessible to the DNA replication machinery. Therefore, in the event that the existing control mechanisms for stopping cell cycle failed, heterochromatin would not be replicated, resulting in a defective daughter cell that will die of apoptosis. Consequently, the cell population will be extinguished rather than being expanded. Areas of heterochromatin are different among different cell types and depend

on their specific differentiation process. Thus, differentiating or differentiated cells cannot be expanded. Accordingly, those skilled in the art would not be motivated to use the knowledge in Xia for solving a cell expansion problem. It is also noted that the above described argument is directed toward Xia relating to a substantially opposite endeavor to the present application. While the present application is concerned with progenitor stem cell expansion ex-vivo or in vitro, Xia relates with non-stem progenitor cell differentiation.

Thus, it is respectfully submitted that Xia does not obviate claims 31-37 of the present application. Accordingly, it is respectfully submitted that the Examiner should withdraw the 35 U.S.C. § 103(a) rejection of claims 31-37.

The Examiner rejects claims 33-35 under 35 U.S.C. § 103(a) as obvious as product-by-process claims under MPEP 2113 over Xia.

The Examiner repeats the law governing product-by-process claims. Product-by-process claims describe a product in terms of the process by which it is obtained. The product claimed in the present application is recited in claim 31 and relates to a culture medium of autologous human progenitor stem cells. However, it is respectfully submitted that claims 33-35 are not product-by-process claims because claims 33-35 are not describing a claimed product on the basis of the process by which it is obtained. That is, claims 33-35 do not recite a product. Specifically, claim 33 relates to an origin in which the autologous human serum is obtained, not a means of creating the autologous human serum. Claims 34-35 relate to a process of obtaining the autologous serum contained in the claimed media, not creating the autologous serum. Those skilled in the art will understand that there are a variety of ways of obtaining autologous serum. However, according to the embodiment recited in claims 34-35, the process of obtaining the autologous serum is via plasmapheresis.

Even if claims 33-35 were considered product-by-process claims, it is respectfully submitted that the Examiner provides an improper basis for rejecting claims 33-35 as product-by-process claims by using Xia. It is noted that the Examiner explicitly states that Xia uses the media composition for a different purpose. (See 7/18/08 Office Action, p. 7). However, the

Examiner attempts to justify this different purpose by stating that "as long [a]s there is a motivation and reasonably expectation of success to arrive at the same concentrations as claimed by Applicant." Applicants would like to stress that the justification for the different purpose relies on the fact that there is a *motivation* to create the product in issue. It is respectfully submitted that modification of the concentrations of heparin or protamine is *not* suggested or implied in Xia. Knowledge in the art of stem cell expansion prior to the submission of the present application would discourage considering Xia or modifications thereof in order to conceive a new cell *expansion* media. Evidence of this discouragement was discussed above. Therefore, in addition to claims 33-35 not being product-by-process claims, it is also respectfully submitted that Xia provides no motivation to arrive at the same concentrations of the product for the present invention.

The Examiner rejects claims 31-40 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent Application No. 2002/0124855 to Chachques in view of U.S. Patent No. 7,015,037 to Furcht et al. (hereinafter "Furcht) in further view of U.S. Patent No. 4,735,726 to Duggins in further view of U.S. Patent No. 6,624,141 to Yang et al. (hereinafter "Yang").

The Examiner correctly states that Chachques does not disclose or suggest the use of autologous human serum, heparin, protamine or the specific concentrations recited in claims 31-40. The Examiner attempts to cure this deficiency with Furcht, Duggins, and Yang. It is noted that Duggins and Yang appear to be relied upon by the Examiner merely to address the deficiency of Furcht regarding a method of collecting the autologous serum from the patient.

The Examiner cites to Chachques by stating that Chachques is related to reducing immune response upon cell transplantation. (See 7/18/08 Office Action, p. 9). The Examiner further asserts that the combination of Furcht is justified because Furcht includes a section relating to the reduction of immune response from transplantation. (See Furcht, col. 28, ll. 61-62). Accordingly, the Examiner's combination of Chachques and Furcht purportedly results in a cell medium that will favour reduction of immune reaction upon transplantation. However, it is noted that Furcht does not disclose or suggest the addition of autologous serum to the culturing media in its discussion of approaches to prevent immune rejection. (See Furcht, col. 28, l. 61 –

col. 29, l. 25). In fact, in Furcht, the addition of autologous serum to the culture media does not appear to be related to the reduction of an immune response upon transplantation. Instead, it appears that the one mention of autologous serum is used simply to maintain the MASCs extracted from bone marrow until used. (See Furcht, col. 15, ll. 40-42). The autologous serum also does not appear to play any other role in Furcht as the autologous serum may be replaced with a varicty of other culture media including calf serum, human AB serum, etc. In addition, Furcht explicitly discloses that the serum is not even necessary for the maintenance of MASCs extracted from the bone marrow. (See Id.). It is respectfully submitted that the Examiner relics upon Chachques and Furcht being combinable based on the reduction of an immune response from transplantation but then finds a disclosure in Furcht where a simple mention of the autologous serum is used. That is, Furcht does not disclose or suggest the use of autologous serum for any other purposc than to maintain the MASCs extracted from bone marrow. Accordingly, it is respectfully submitted that those skilled in the art would not obviate the use of autologous serum for reducing immune rejection based upon the entire disclosure of Furcht.

Thus, it is respectfully submitted that neither Chachques, Furcht, Duggins, nor Yang, either alone or in combination, discloses or suggests an "autologous expansion culture medium of autologous human progenitor stems cells" comprising" "between 0.1% and 90% weight of autologous human serum," as recited in claim 31. Accordingly, it is respectfully submitted that claim 31 is allowable and the Examiner should withdraw the 35 U.S.C. § 103(a) rejection for this claim. Because claims 32-40 depends from and, therefore, includes all the limitations of claim 31, it is respectfully submitted that these claims are also allowable.

Furthermore, it is noted that bone marrow cells are not the same type of cells exemplified in the present application which are muscle progenitor CD56+/CD45- cells. Those skilled in the art will understand that different cells display different responses to a common cell factor. For example, heparin is a differentiating factor for monocytes while it does not have any effect on muscle cells. Thus, it is respectfully submitted that Furcht does not relate to the same field of endeavor as the present application and the combination of Chaachques and Furcht is misplaced.

The Examiner rejects claims 31-40 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,472,212 to Valerio et al. (hereinafter "Valerio") in view of U.S. Patent No. 5,817,773 to Wilson et al. (hereinafter "Wilson").

Initially, the Examiner asserts that the combination of Valerio with Wilson teaches an expansion of bone marrow cells. However, as discussed above with reference to the combination of Chachques and Furcht, bone marrow cells are not the same type of cells exemplified in the present application. Thus, the combination of Valerio with Wilson to address the recitation of claims 31-40 is misplaced as the references relate to a different field of endeavor than the present application.

In addition, the problem purportedly addressed in Valerio is to increase gene transfer. (See Valerio, abstract). Cells in Valerio are transduced cells which those skilled in the art will understand have specific requirements. Thus, the media contemplated by Valerio is a transduction media. In fact, a few factors are added to this media in order to potentiate gene transfer such as polybrene, protamine sulphate, and protamine-HCl. For these further reasons, it is respectfully submitted that at least Valerio relates to a different field of art, thereby belonging to a different technical field to that of the present application.

Furthermore, it is noted that rejections under 35 U.S.C. § 103(a) include basic criteria for a prima facie case of obviousness. For example, there must be a reasonable expectation of success. In another example, the prior art references must teach all the claim limitations. (In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Initially, it is again noted that those skilled in the art would not reasonably be led to take the teachings of Valerio and modify them with the teachings of Wilson. Those skilled in the art will understand that the expansion of CD56+/CD45- progenitor stem cells is not analogous with bone marrow (CD34+) progenitor cells. The improper combination of Valerio with Wilson is further evidenced by the contradictory teachings contained therein if combined. Valerio uses protamine to increase the rate of gene transfer. However, as taught by Wilson, the addition of heparin would render the teachings of Valerio invalid for its intended use because protamine and heparin are antagonists and neutralize each other. Therefore, it is respectfully submitted that there is no reasonable

expectation of success when viewing the specific use of protamine in Valerio with the specific use of herpain in Wilson since they would be used in combination according to the Examiner's combination.

Thus, it is respectfully submitted that the Examiner improperly combined the teachings of Valerio with the teachings of Wilson. Accordingly, it is respectfully submitted that claim 31 is allowable and the Examiner should withdraw the 35 U.S.C. § 103(a) rejection for this claim. Because claims 32-40 depend from and, therefore, include all the limitations of claim 31, it is respectfully submitted that these claims are also allowable.

It is further noted that the bone marrow cells do not express the surface marker of the muscle lineage CD56 unless they are carcinogenic. Those skilled in the art will understand that carcinogenic cells may not be used for cell transplantation. That is, to use the teachings from the combination of Valerio and Wilson would again be contrary to conventional knowledge to those skilled in the art.

CONCLUSION

In light of the foregoing, Applicants respectfully submit that all of the now pending claims are in condition for allowance. All issues raised by the Examiner having been addressed, and an early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

Dated: December 20, 2008

By: _____
Oleg F. Kaplun, Esq. (Reg. No. 45,559)

Fay Kaplun & Marcin, LLP
150 Broadway, Suite 702
New York, NY 10038
Tel: (212) 619-6000
Fax: (212) 619-0276